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TXR # 0011636

REPORT

STUDY TYPE: 21-Day Dermal Toxicity **GUIDELINE: 82-2**

PC CODE: 128931 **MRID No.** 435542-06

TEST MATERIAL: **Diglycolamine** Salt of Dicamba

REGISTRANT: Sandoz Crop Protection, Des Plaines, IL.

TESTING LABORATORY: Pharmaco LSR, Inc., East Millstone, NJ.

STUDY IDENTIFICATION: 94-2326

TITLE OF REPORT: *"A REPEATED DOSE (21-DAY) DERMAL TOXICITY STUDY OF DGA SALT OF DICAMBA IN THE RABBIT".*

AUTHOR: Donna Blaszczak

REPORT DATE: November 23, 1994

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID No. 435542-06) New Zealand White rabbits [5/sex/dose] were given repeated dermal applications of the diglycolamine salt (59%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week for a total of 15 applications during a 3 week period. No treatment-related dermal reactions or histopathological dermal lesions were seen. No systemic toxicity was seen; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology. **Based on the results of this study, a NOEL of 1000 mg/kg/day (Limit-Dose) was established for both dermal irritation and systemic toxicity. A LOEL was not established for either end-point.**

CORE CLASSIFICATION: This study is classified as **Core Guideline** and satisfies the data requirement [§82-2] for a 21-day dermal toxicity study in rabbits and is acceptable for regulatory purposes.

I. INTRODUCTION

This Data Evaluation Report summarizes the experimental procedures and results of a 21-day dermal toxicity study of the diglycolamine salt of dicamba (DGA of Dicamba) in rabbits.

II. MATERIALS AND METHODS

1. Test Material

Name: Diglycolamine salt of dicamba
Active Ingredient: 58.56% DGA
Dicamba Equivalent: 39.7%
Lot No.: 5998-1
Description: Amber liquid

2. Test Animals

Species: Rabbit
Strain: New Zealand White Hra:(NZW) SPF
Sex: Males and females
Age: Approximately 4 to 5 months at initiation
Weight: 2.4 to 2.8 kg (M) & 2.4 to 2.9 kg (F) at initiation
Identification: Ear tags
Acclimation: Approximately 3 weeks
Health Status: Good
Housing: Individually in suspended wire mesh cages
Food: Certified Lab Rabbit Chow HF#5325 ad libitum
Water: Tap water ad libitum
Environment: Temperature, 55 to 73°F; Humidity, 50 to 80%; Light cycle- 12 hr. on/off.

3. Study Design

Group No./Treatment	No. of Animals Males	Females	Dose Level (mg/kg/day)
1 (vehicle control)	5	5	0
2 (Low-dose)	5	5	100
3 (Mid-dose)	5	5	500
4 (High-dose)	5	5	1000

4. Test Material Formulation

The test material was administered neat as received.

5. Treatment

Approximately 24 hours prior to dosing, the hair was clipped from the dorsal region (about 12 x 14 cm) of each rabbit to cover an area of approximately 10 % of the total body surface. The appropriate dose of the test material, calculated on the basis of the most recent weekly body weight, was applied to the clipped skin of each rabbit and spread as uniformly as possible over the application site. The dosing volumes were 0.08 ml/kg, 0.41 ml/kg and 0.81 ml/kg for the 100 mg/kg, 500 mg/kg and 1000 mg/kg, respectively. The test site was covered by gauze which was held in place by an adhesive bandage wrapped around the trunk (semi-occlusive). Control rabbits were sham treated. Elizabethan collars were placed on all animals and worn throughout the study to allow animal mobility, while preventing test material ingestion. Rabbits received the test material for 6 hours/day, 5 days/week for a total of 15 applications during a 21 day interval.

7. Experimental Procedures

Parameter	Time measured
Mortality and Moribundity	Twice daily
Clinical signs	Weekly
Dermal irritation	Daily prior to dosing (Draize Scoring)
Body weight	Twice prior to dosing and weekly thereafter
Food consumption	Not measured only estimated
Hematology and Clinical Chemistry	At pretest and termination

Hematology

x Hematocrit	x Leukocyte count (WBC)
x Hemoglobin (HGB)	x Platelet count
x Erythrocyte count (RBC)	x Mean corpuscular volume (MCV)
x Mean corpuscular hemoglobin concentration(MCHC)	x Prothrombin time
x Activated partial thromboplastin time	x Leukocyte differential

Clinical Chemistry

x Albumin	x Creatinine
x Blood Urea Nitrogen	x Glucose
x Aspartate aminotransferase (AST)	x Globulin
x Alanine aminotransferase (ALT)	x Total Protein
x Alkaline phosphatase	x Total Bilirubin
x Sodium	x Chloride
x Calcium	x Potassium
x Inorganic Phosphorous	

8. Termination

At termination, surviving animals were weighed, and sacrificed (sodium pentobarbital) and were subjected to a complete necropsy. Necropsy included observations of all external surfaces, orifices and cranial cavity, the external and cut surfaces of brain, all viscera and glands, and the carcass. **Brian, kidneys, liver, ovaries and testes/epididymides were weighed** and organ-to-body weight ratios were calculated.

9. Histopathology

Histopathology included skin (treated and untreated), liver, kidneys and gross lesions from all control and treated animals as well as the gross lesions from the low- and mid-dose groups.

10. Statistical Analyses

All parameters examined were analyzed using parametric (ANOVA, and Dunnett's test) and nonparametric (Kruskal-Wallis and Dunn's Rank Sum) procedures. Statistical evaluation of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First Bartlett's test was performed to determine if groups had equal variance. If variances were equal, parametric procedures were used; if not nonparametric procedures were used.

11. Regulatory Compliances

A signed and dated (2/13/95) statement of No Data Confidentiality Claim was provided. A signed and dated (2/13/95) statement indicated that this study was conducted in accordance with the principles of EPA's Good Laboratory Practices [40 CFR.160]. A signed and dated (9/14/94) Quality Assurance statement was provided that was dated

8/6/93.

III. RESULTS

1. Survival

No mortalities occurred.

2. Clinical Signs

No treatment-related clinical signs of toxicity were observed during the study.

3. Dermal Observations

No dermal irritation was seen in the control animals. On Day 7, very slight/slight erythema was observed in 2 males and 3 females at 100 mg/kg/day, 1 male at 500 mg/kg/day and 2 males and 4 females at 1000 mg/kg/day. On Day 14, very slight erythema was seen in 1 male at 100 mg/kg/day, 1 male and 2 females at 500 mg/kg/day and none at the high dose. On Day 21, very slight erythema was seen in 1 male and 2 females at 500 mg/kg/day; no dermal irritation was seen at the high dose.

4. Body Weight/Body Weight Gain

No treatment-related effects were seen either in mean body weights or body weight gains in at any dose level. Mean body weight data are presented in Table 1.

Table 1. Mean Body Weight (KG) in Rabbits Receiving Dermal Applications of DGA Dicamba.

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	100	500	1000	0	100	500	1000
0	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
1	2.5	2.5	2.5	2.5	2.5	2.6	2.6	2.6
2	2.7	2.7	2.6	2.7	2.6	2.7	2.6	2.6
3	2.6	2.6	2.6	2.6	2.6	2.7	2.6	2.7

5. Clinical Pathology

No biologically significant or treatment-related changes were seen in mean hematology and clinical chemistry values in treated groups when compared to the vehicle control group values. The statistically significant ($p < 0.05$) increase in the mean prothrombin time of males at 100 mg/kg/day (5.7 seconds) compared to control males (5.2 seconds) and the significant decrease in the mean albumin/globulin ratio of the females at 1000 mg/kg/day (2.3) compared to control females (2.9) were not considered to be biologically significant or treatment-related due to a lack of dose-response and individual values fell within the normal range of this strain/age of rabbits.

6. Gross Pathology

No treatment-related gross pathological changes were seen at termination.

7. Organ Weight

Organ weight data were comparable between the treated and control groups.

8. Histopathology

No treatment-related histopathological lesions were seen in the treated skin, liver and kidneys at any dose levels.

IV. DISCUSSION

Male and female rabbits received repeated dermal applications of the diglycolamine salt of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week for 3 weeks (15 applications). No treatment-related dermal reactions or histopathological dermal lesions were seen. No systemic toxicity was seen; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology.

V. CONCLUSION

Based on the results of this study, a NOEL of 1000 mg/kg/day (Limit-Dose) was established for both dermal irritation and systemic toxicity. A LOEL was not established for either end-point.

VI. CORE CLASSIFICATION

Guideline; this study satisfies the data requirement [§82-2] for a 21-day dermal toxicity study in rabbits and is acceptable for regulatory purposes.

PC Code: **128931** _____ File Last Updated _____ Current Date _____

Diglycolamine salt of Dicamba

STUDY/LAB/STUDY #/DATE	MATERIAL	EPA MRID NO.	NOEL, LEL	TOX CATEGORY	RESULTS: LD50, LC50, PIS, CORE GRADE/DOC. #
82-2 21-Day Dermal Tox. Species: NZW Rabbits Pharmacon LSR 94-2326;11/94	Diglycolamine salt of dicamba 58.56% DGA 39.7% dicamba	435542-06	Dose levels: 0, 100, 500, 1000 mg/kg, 6 hrs/day, 5 days/week for 3 weeks (15 applications). No treatment-related dermal reactions or histopathological dermal lesions were seen. There was no systemic toxicity; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology. Dermal Irritation NOEL = 1000 mg/kg/day (Limit-Dose) Dermal Irritation LOEL = Not established Systemic Toxicity NOEL = 1000 mg/kg/day (HDT; LOEL = Not established	NA	Guideline RR